Conferences and Reviews

Long-Range Safety and Protective Benefits of Angiotensin-Converting Enzyme Inhibitors for Hypertension

Do We Need More Clinical Trials?

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Inhibition of the renin-angiotensin system is being applied with considerable success to the treatment of hypertension and heart failure. Angiotensin-converting enzyme (ACE) inhibitors are the only currently available agents that can achieve this objective. In general, the major therapeutic effects of these agents in the treatment of mild to moderate hypertension or of heart failure are exerted on the vascular tissue through inhibition of the renin-angiotensin system and, secondarily, of the sympathetic nervous system. When cardiovascular functional reserve is diminished and autoregulation of regional and systemic blood flow is strained, however, ACE inhibitors may affect other organ functions (heart, kidneys, and possibly brain), hormones other than the renin system, and local tissue humoral systems. The interrelations between the renin-angiotensin system and several other vasoactive systems—including circulating and locally generated tissue hormones and centrally acting neurohormonal factors—are complex and unclear. A better understanding of these mechanisms and interrelations would allow for a more rational therapeutic use of these agents. Unknown also are the clinical effects of prolonged ACE inhibition. Whether the use of ACE inhibitors can provide primary cardiorenal protection requires proof through definitive clinical trials.

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MOHINDER P. SAMBHI, MD, PhD*: The introduction of angiotensin-converting enzyme (ACE) inhibitors as new therapeutic tools for hypertension and for heart failure has, in many ways, revolutionized the treatment of these cardiovascular disorders. Certain fundamentally important questions, however, remain. Do we know all we need to know about the mode of action of these drugs? Can they protect against long-term cardiovascular-renal damage, as has been claimed?[1] Or do we need future well-designed and well-controlled clinical trials—despite their inherent limitations—to answer these crucial questions? In this rapidly evolving area, the present discussion cannot provide unequivocal or comprehensive answers, but it does provide a perspective from clinical investigators who have directed their attention over the years to this research area.

Elucidating the precise mode of action of ACE inhibitors promises to fill in some gaps in our knowledge of the pathophysiology of hypertension and of heart failure. More specifically, such knowledge might clarify the functional importance of the endocrine actions (circulating angiotensin II) versus the paracrine and autocrine actions (effects on neighboring and same cells of locally produced angiotensin II) of the renin-angiotensin system in health and disease. The development of therapeutic tools—better ACE inhibitors, specific inhibitors of the enzyme renin, or specific receptor antagonists for angiotensin—derives its impetus from the same rationale. Angiotensin-converting enzyme inhibitors lower blood pressure in hypertension or lower afterload in heart failure predominantly by inhibiting angiotensin activity and, secondarily, sympathetic nervous activity. It is not clear, however, in which organs and tissues this inhibition is of greatest importance.

When ACE (kininase II) activity is suppressed, vasoactive kinins accumulate and may mediate certain metabolic consequences, such as improved insulin sensitivity.[2] In animals, the local vasodilatory actions of kinins may contribute to the antihypertensive potential of ACE inhibitors,[3] but this has not as yet been shown to pertain in the clinical use of these agents.

Angiotensin can be produced locally in several tissues.[4] Tissue renin-angiotensin systems, controlled independently of the circulatory system, may exist. For example, measurable amounts of essential components of the system are found

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ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
HAPPHY = Heart Attack Primary Prevention in Hypertensives
HDFP = Hypertension Detection and Follow-up Program
IPPPSH = International Prospective Primary Prevention Study in Hypertension
MAPHY = Metaprolol Atherosclerosis Prevention in Hypertension
MRFIT = Multiple Risk Factor Intervention Trial
VA = Department of Veterans Affairs

in tissues, as well as constitutive gene expression of system proteins.[4] This evidence for functionally distinct renin systems in different tissues remains largely circumstantial, however.

Does angiotensin have a normal paracrine or autocrine function—as distinguished from its endocrine function—in various tissues? Such a putative role has not been established for normal or for pathologic states. The endocrine effects of circulating angiotensin II can be measured readily in the whole organism, but the possible tissue-specific paracrine and autocrine effects of locally produced angiotensin II would be selective for the individual organ systems. In cardiac tissue an enzymatic pathway, independent of ACE activity, is capable of generating angiotensin II. Angiotensin-converting enzyme inhibits peripheral resistance by suppressing angiotensin activity in vascular tissue, but it may not substantially affect angiotensin formation in cardiac tissue.[5] Thus, despite ACE inhibition, a failing heart may benefit from the possible inotropic actions of undiminished, or even increased, locally produced angiotensin, compensatory to afterload reduction.[6]

It can be predicted that inhibiting ACE production may be beneficial if the renin-angiotensin system is overactive. Conversely, inhibiting ACE production may be deleterious if a compensating, protective function is being performed by the renin-angiotensin system. For example, in bilateral renal artery stenosis, autoregulation of the glomerular filtration rate and renal blood flow depends entirely on the availability of intrarenal angiotensin. If ACE activity is inhibited, therefore, renal function will be impaired. How do ACE inhibitors affect patients with normal or low renin levels? Angiotensin contributes to the physiologic regulation of blood flow and of organ perfusion as one part of an integrated functional reserve for homeostasis. These overall homeostatic mechanisms can break down and adversely affect the use of ACE inhibitors. For example, if there is severe sodium depletion or volume contraction, inhibiting ACE may result in dangerous hypotension. It is not known whether prolonged ACE inhibition may be deleterious from a deficiency either of the angiotensin generated locally in the tissue renin-angiotensin system or that produced in the circulation.

Is the considerably higher cost of newer ACE inhibitors justified? Can we use cheaper drugs without impairing the long-term cardiovascular and renal protective effects claimed for ACE inhibitors? Industry should assume the major responsibility for funding clinical trials to answer these highly relevant questions.

Mode of Action

HARALAMBOS GAVRAS, MD*: Angiotensin-converting enzyme inhibition is now widely accepted as a first-line approach to treating hypertension and congestive cardiac failure. Numerous experimental and clinical studies of hemodynamic, hormonal, and metabolic effects of various ACE inhibitors conclusively show the advantages of this treatment over other pharmacologic therapies in safety, tolerability, cardioprotection, and patient convenience. Yet, despite more than two decades of intensive research, the exact mode of action of ACE inhibitors remains incompletely understood. In this section I review the mechanisms by which ACE inhibitors are thought to lower the blood pressure.

The era of ACE inhibition started when Ferreira discovered in the venom of a Brazilian snake (*Bothrops jaracaca*) a series of polypeptides that potentiated the effects of bradykinin by inhibiting its enzymatic degradation, hence named bradykinin-potentiating factors.[7] Shortly thereafter, it was discovered that the enzyme that converts angiotensin I to angiotensin II is identical to the kinase II that metabolizes bradykinin.[8] Therefore, ACE inhibition should theoretically interrupt the formation of the vasoconstrictor angiotensin II and lead to an accumulation of the vasodilator bradykinin; both actions should relax blood vessels and reduce blood pressure. As anticipated, when these polypeptides were administered to animals with experimental renovascular hypertension (which is typically angiotensin-dependent) blood pressures fell.[9]

When the first synthetic ACE inhibitor suitable for human use, teprotide, was given intravenously, plasma ACE activity was virtually eliminated within minutes. As a result, angiotensin II was notably suppressed as was plasma aldosterone, whose secretion depends in part on stimulation by angiotensin II of the adrenal zona glomerulosa. Patients with renin-dependent hypertension, such as those with renovascular or malignant hypertension, had a considerably greater decrease in blood pressure than did patients with low-renin essential hypertension.[10] Suppression of aldosterone secretion in high renin states should also contribute to lowering blood pressure by diminishing renal tubular reabsorption of sodium and thus attenuating the vasopressor consequences of excessive sodium retention.

Subsequent short- and long-term studies with the oral ACE inhibitor captopril[11-14] permitted a better evaluation of its hormonal effects. In short-term studies, plasma ACE activity was suppressed after each dose but returned to baseline within about two hours, even though blood-pressure lowering was maintained for six to eight hours. Moreover, after a few days or weeks of ACE inhibition, circulating levels of plasma angiotensin II and aldosterone tended to rise toward baseline, even though antihypertensive action was sustained. More important, in the first few patients, this action did not correlate with baseline renin levels. Subsequently, in large groups of patients, the weak correlation between pretreatment levels of plasma renin activity (a reflection of circulating angiotensin II and an index of the degree of angiotensin II dependency of a given blood pressure level) and the magnitude of blood pressure fall after ACE inhibition became statistically significant, but individual variability resulted in frequent overlap. Indeed, some patients with low-renin hypertension showed a substantial antihypertensive response that tended to be further accentuated with time. It became clear that baseline levels of plasma renin activity could not fully predict a patient's response to the drug.

Why does this dichotomy exist? Some investigators postulated that ACE inhibition affected not only circulating an-

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giotensin II levels but also local angiotensin II generation within the vascular wall. Components of the renin-angiotensin system are known to exist in various tissues, including the vessel wall and the brain,[15-17] and may play an important role in cardiovascular homeostasis. Inhibiting ACE, however, fails to decrease blood pressure in nephrectomized animals. Additional hypotensive mechanisms are clearly involved.

In a comparative study, teprotide was found to have a greater hypotensive action than did another angiotensin II antagonist, saralasin.[18] A partial agonistic activity of saralasin might explain some of this difference. Captopril, however, was found to elicit a considerable antihypertensive response even in patients whose blood pressure failed to decrease despite a total inhibition of plasma renin activity by the use of a specific renin inhibitor.[19] Thus, it appears far more likely that the difference in response resulted from an additional blood pressure-lowering mechanism when ACE was inhibited. One such mechanism is suspected to be the potentiation of bradykinin, but bradykinin has not been clearly demonstrated to accumulate in plasma during ACE inhibition.[20-22]

The most conclusive results were ultimately obtained by blocking the action of bradykinin by antibodies or specific antagonists. Using specific antibodies to bradykinin, bradykinin was shown to participate in the blood-pressure lowering produced by ACE inhibition.[23] In studies using competitive vascular antagonists of bradykinin[24] in renovascular hypertensive rats, we concluded that about a third of the hypotensive effect of enalapril was attributable to bradykinin.[25] Several studies using other ACE inhibitors or other bradykinin antagonists have confirmed these findings.[26,27]

Agents that antagonize vascular bradykinin receptors may also have partial agonistic properties for other bradykinin receptors, especially those in sympathoadrenal tissues.[28] Moreover, bradykinin exerts its vascular effects through β_1 and β_2 receptors and possibly additional unidentified receptors.[29] Some of these have direct effects on vascular smooth muscle, whereas others act by stimulating other vasoactive substances like endothelium-derived relaxation factor and prostaglandins. Therefore, it is complex to assess the relative contributions of bradykinin itself and those of the several other systemic and tissue hormones that it regulates to the blood pressure-lowering effects of ACE inhibition. Nevertheless, bradykinin is now generally thought to play a contributory role. The finding that excess body sodium suppresses the generation of kinins[30] further explains the loss of antihypertensive efficacy of ACE inhibitors after salt loading.

Another mechanism appears to participate in the long-term antihypertensive effect of ACE inhibition, that of the influence of the long-term blockade of angiotensin II formation on other vasopressor systems. All three major vasopressor systems—renin-angiotensin, sympathoadrenal, and vasopressin—are closely interrelated through neurohormonal pathways. Each pathway transmits positive or negative feedback to one or more of the others, affecting its release or responsiveness by acting as a neurotransmitter or neuromodulator or by exerting a permissive action on effector organs. For example, angiotensin II stimulates the release of catecholamines and vice versa. Long-term ACE inhibition blunts the pressor response of arterioles to sympathetic stimuli.[31] It also diminishes sympathetic activity, as evidenced by decreased levels of circulating norepinephrine and decreased turnover and tissue content of norepinephrine.[32] In this respect, ACE inhibitors exert pharmacologic effects opposite to those of other vasodilators, such as hydralazine or minoxidil, which cause reflex stimulation of the sympathetic system.

The clinical implications of these differences are important, as they may explain some of the different long-term effects of these drugs in various tissues. For example, ACE inhibitors can reverse hypertension-induced left ventricular hypertrophy,[33] whereas other vasodilators with equally good antihypertensive efficacy cannot. As another example, ACE inhibitors can reduce mortality in chronic congestive heart failure,[34] whereas most other vasodilators that successfully control symptoms of congestive heart failure do not seem to prolong life.[35] A hydralazine-nitrate combination did reduce mortality but was still less effective than enalapril.[36]

Vasopressin, on the other hand, appears to function as an important vasoconstrictor only when the renin-angiotensin and sympathetic nervous systems are effectively obliterated. Angiotensin II facilitated the release of vasopressin in response to stimuli, and captopril decreased plasma vasopressin levels.[37]

In general, changes in the release of or responsiveness to one factor lead to compensatory adjustments in plasma or tissue levels or receptor sensitivity of the others. Angiotensin-converting enzyme inhibition affects all these interdependent functions, which probably contributes to the final blood pressure response, the magnitude of which varies under various clinical conditions.

Possible Cardiac and Renal Problems

J. I. S. ROBERTSON, MD*: The therapeutic efficacy of ACE inhibitors is well established.[38] They lower blood pressure predictably in patients with renovascular hypertension and, when combined with a loop diuretic, in those with severe and often resistant hypertension. Moreover, they can work effectively in treating essential hypertension, administered either alone or with a thiazide diuretic. In cardiac failure, they have diminished dyspnea, improved exercise capacity, reduced the prevalence of ventricular ectopic rhythms,[39] and prolonged survival.[34]

The side effects of ACE inhibitors are also well established.[38,40] Some problems apparently specific to captopril may relate to the thiol group in that compound; these problems were more prominent in the early days of therapy when unsuitable high doses of as much as 450 mg per day were used. The initial problems included neutropenia, agranulocytosis, proteinuria, the nephrotic syndrome, and Guillain-Barré neuropathy. These complications have receded with reduced doses of no more than 150 mg per day and further reduced doses in patients who have renal impairment. Nevertheless, taste loss or disturbance does remain a problem with captopril therapy, even at current lower doses, but it may occur less frequently. Guillain-Barré neuropathy has also been reported with the use of captopril at a dose of only 75 mg per day.[41] Side effects with ACE inhibitors as a class include morbilliform or urticarial rash, unproductive cough, occasional wheezing, angioneurotic edema, Raynaud's phenomenon, headache, dizziness, and syncope.[38,40]

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My principal concern here is not with the side effects of ACE inhibitors as such but rather with physiologic consequences inherent in the pharmacologic actions of these drugs. I shall consider such problems related to two organs, the heart and the kidneys.

Cardiac Effects

In both normotensive and hypertensive patients, circulating concentrations of angiotensin II are within a range having a direct, immediate effect on arterial blood pressure.[42] Thus, lowering angiotensin II levels with the initial dose of an ACE inhibitor was found to cause prompt and proportionate blood pressure reduction, significantly correlated with levels of renin or angiotensin II before therapy and with the fall of plasma angiotensin II levels at the early peak effect of the drug.[38,43] With more prolonged therapy, these correlations become looser,[38,43] as discussed by Dr Gavras earlier. Such consistent effects of the first dose raise clinical concern in patients with hypertension only when ACE inhibition therapy is introduced in those with high circulating angiotensin II levels, as with previous diuretic treatment[44] or in the hyponatremic hypertensive syndrome.[45] Angiotensin-converting enzyme inhibitors can then cause an initial steep, profound drop in arterial pressure, sometimes enough to imperil the cerebral circulation.

A rarer, less predictable, but potentially more serious problem relates to two other actions of angiotensin II, its facilitating action on the sympathetic nervous system[31] and its converse vagolytic effect.[46] The sudden and simultaneous removal of both of these actions with ACE inhibition can provoke severe hypotension, syncope, and bradycardia. An additional contributory factor, activation of the Bezold-Jarisch reflex,[47] has also been proposed. These events are especially likely when ACE inhibition is introduced in patients with cardiac failure, a condition resulting in sympathetic activation and, particularly if digitalis is administered, in potentially high vagal tone. The fall in blood pressure in these patients significantly correlates with the plasma angiotensin II concentration before ACE inhibition and with the subsequent fall in heart rate.[48] With syncope of this cause, plasma epinephrine levels increase, indicating stimulation of adrenal medullary secretion but no rise in the concentration of plasma norepinephrine.[49] First-dose hypotension has been regularly encountered in all the major trials of ACE inhibitors in cardiac failure, including the Cooperative North Scandinavian Enalapril Survival Study,[34] the second Vasodilator-Heart Failure Veterans Affairs Cooperative Study Group,[36] and the Studies of Left Ventricular Dysfunction.[50]

This sometimes disturbing syndrome has been treated by atropine sulfate administration and intravenous angiotensin II infusion.[48] It may, if uncontrolled, lead to cerebral, renal, or cardiac damage. Because the occurrence of the syndrome is not readily predictable, the use of a short-acting ACE inhibitor, such as captopril,[1] rather than a longer-acting one, such as lisinopril, enalapril, or ramipril, has been recommended. This approach will not prevent the occurrence but will facilitate treatment by limiting its duration. An alternate approach has been to reduce the initial dose of the ACE inhibitor.[34]

Renal Effects

Angiotensin II has potent, presumably important local actions on the kidneys. One route of its access to renal tissues is through renal arterial blood. In addition, all components of the renin-angiotensin system are present in the kidneys,[51,52] and locally generated angiotensin II can gain access to intrarenal structures in both renal blood and renal lymph. The latter routes could well be the more important.

Angiotensin II has been found in both afferent and efferent glomerular arterioles.[51] There is evidence that the efferent arterioles are disproportionately sensitive to the vasoconstrictor effects of angiotensin II.[53] Its receptors are especially profuse about the glomeruli and over the vasa recta bundles.[54] Two possible intrarenal functions of angiotensin II may be especially important when renal blood flow is imperiled. First, differentially enhanced tone at efferent arterioles helps to sustain the glomerular filtration rate despite a decreased renal blood flow.[53,55,56] Second, angiotensin II-mediated slowing of blood flow in vasa recta bundles could facilitate a countercurrent exchange between the descending arterial and the ascending venous limbs and between the ascending venous limbs and the descending thin limbs of the loops of Henle. This second function could be an important means of preserving urea excretion.[55,56] Although such functions are compensatory, a gross excess of local angiotensin II could clearly cause a shutdown of the circulation by both the glomeruli and the vasa recta and a rapid advance into renal failure.

Clinical Implications

Features common to three clinical syndromes—cardiac failure, sodium depletion, and renal artery stenosis—may activate the initially compensatory intrarenal actions of angiotensin II.[56,57] All three syndromes are often accompanied by elevated peripheral plasma concentrations of renin and angiotensin II. Moreover, renal blood flow is reduced; it is probable, but not demonstrated, that this diminished blood flow mainly traverses the deep nephrons. Initially, all three syndromes share a partial preservation of the glomerular filtration rate and a capacity to secrete urea. In renal artery stenosis, increased intrarenal renin sustains the renal arterial pressure distal to the stenosis.[58] All three conditions may terminate in renal failure, characterized by a pronounced rise in serum urea and creatinine levels and a fall in the serum sodium concentration. In renal artery stenosis, however, renal failure develops only if both kidneys are affected, if one kidney is absent, or if the rare hyponatremic hypertension syndrome is present.[45]

The normal gradient of renin across the kidney is lost in both renal artery stenosis[59] and sodium depletion.[60] The normally renin-poor deep glomeruli become rich in renin as the overall renin content of the kidneys increases. Although similar changes probably occur in cardiac failure, this phenomenon has yet to be studied. Renin appears in the deep nephrons at a time when renal performance comes to rely principally on these structures and when renal functional compensation evidently depends heavily on a local intrarenal action of angiotensin II.

If the foregoing speculations prove valid, then any clinical benefits accruing from ACE inhibition in cardiac failure or renal artery stenosis will, in most cases, be associated with some inevitable adverse renal consequences.[56,57] In patients with pure sodium depletion, ACE inhibitors could be predicted to be entirely harmful[61] and should not be given. In most cases of cardiac failure, ACE inhibitors do produce a range of benefits, as enumerated earlier; however, their use is

predictably accompanied by a consistent rise in serum urea and creatinine levels[36,39,50] for reasons explained earlier. Rarely, however, in a preterminal patient who presumably already has grossly excessive intrarenal renin, markedly elevated urea and creatinine levels, and hyponatremia, administering ACE inhibitors can understandably improve renal function and correct the hyponatremia.[62] In renovascular hypertension, ACE inhibitors can effectively control the elevation of systemic arterial pressure[43,57] and correct the pronounced biochemical abnormalities of the hyponatremic hypertensive syndrome.[45] The already impaired functioning of the afflicted kidney frequently worsens, however, with a fall in the glomerular filtration rate[63] and renal plasma flow.[57] In some patients, ACE inhibition may provoke renal artery occlusion.[57] In experimental renal artery stenosis in rats, ACE inhibition causes an already small poststenotic kidney to shrink further.[64]

Is the Role of Cardiovascular Risk Reduction Established in Hypertension?

WILLIAM MCFATE SMITH, MD, MPH*: Whether reducing cardiovascular risk factors lowers blood pressure is a question that is confounded by the implied assumption that the treatment of hypertension with ACE inhibitors has been shown to reduce risk. In the absence of such evidence, we must confront a compelling question: Must definitive trials be mounted to show that ACE inhibitors when used to treat hypertension reduce morbidity and mortality? Several subsidiary issues surround that question (not all of which will be addressed here):

- What is the standard—how effective are other agents in reducing morbidity and mortality?
- What evidence shows that blood pressure control per se reduces risk? and for which end points?
- Do ACE inhibitors have effects other than lowering blood pressure?
- Is there reason to think that a drug could lower blood pressure without reducing risk?
- How good is the evidence that blood pressure control lowers risk?
- Has this been shown for all other antihypertensive agents? Must it be?
- Are these issues only regulatory? or are they also scientific?

Diuretics and β-Blockers

We must first examine the evidence that pharmacologic lowering of blood pressure reduces the risk of cardiovascular complications in patients with mild to moderate hypertension. In 1986, MacMahon and co-workers reviewed designs and the results of 19 controlled studies with data on morbidity and mortality, including nine long-term, randomized, controlled trials published in the preceding seven years.[65] They assessed the consistency of these studies, measured changes in cardiovascular morbidity and mortality resulting from the drug treatment of hypertension, and analyzed pooled results from the nine most relevant studies.

The analysis of pooled results had a twofold rationale. First, most studies were designed to recognize treatment efficacy for combined cardiovascular disease end points, and event rates in individual studies were only sufficient to detect large treatment effects, such as those seen for cerebrovascular disease. Second, the size and event rates of most individual studies were inadequate to determine small (10% to 15%) reductions in either total mortality or fatal and nonfatal ischemic heart disease. Unlike the analysis of any single study, the analysis of pooled results provided more stable estimates of effects of treatment and greater power to detect relatively modest reductions in morbidity and mortality.

Pooled data were analyzed by calculating the difference between observed and anticipated events (treated versus control groups) and the variance of that difference for each trial and then summing results for all trials.[66] From these values, an odds ratio (z value) and 95% confidence intervals were calculated and were expressed in terms of percent change in risk.

The pooled analysis was based on about 43,000 patients with an average follow-up of 5.6 years. Sample sizes varied from 380 in the VA study[67] to more than 17,000 in the Medical Research Council trial.[68] Follow-up ranged from 1.5 years in the VA–National Heart, Lung and Blood Institute trial[69] to 7.5 years in the US Public Health Service Hospitals study.[70]

In these studies, the lowering of diastolic blood pressure was nearly 6 mm of mercury greater in the intervention than in control groups. Criteria for end points were assumed to be comparable in the pooled studies. Whereas comparability is certain for total mortality, it is less certain for cause-specific mortality or morbidity due to such causes as nonfatal myocardial infarction.[67-73] The two studies without untreated controls—the Hypertension Detection and Follow-up Program (HDFP)[74] and the Multiple Risk Factor Intervention Trial (MRFIT)[75]—differed from the others in that their con-

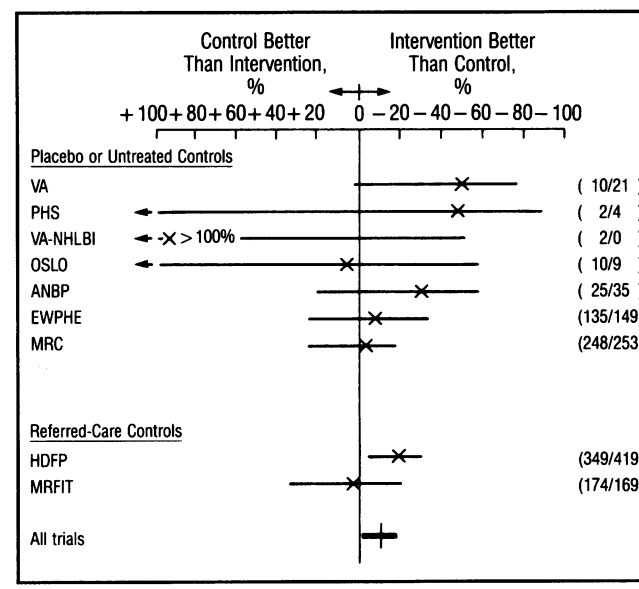

Figure 1.—Estimates, with approximate 95% confidence intervals, are shown for the relative difference in total mortality between intervention and control groups. The number of events (intervention/control) is given in parentheses (from MacMahon et al[65]). ANBP = Australian National Blood Pressure Study, EWPHE = European Working Party on High Blood Pressure in the Elderly, HDFP = Hypertension Detection and Follow-up Program, MRC = Medical Research Council Working Party, MRFIT = Multiple Risk Factor Intervention Trial, OSLO = Oslo Trial in Mild Hypertension, PHS = US Public Health Service Hospitals Cooperative Study Group, VA = Veterans Administration, VA-NHLBI = Veterans Administration–National Heart, Lung, and Blood Institute

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trol subjects received the standard treatment of their respective communities. Inclusion of HDFP and MRFIT was justified on the basis that it could only lead to underestimating treatment benefits.

In five of the seven studies with placebo or untreated controls, intervention lowered total mortality, but the reduction was statistically insignificant (Figure 1). The VA and Australian studies showed the strongest trends in reduced mortality. On the other hand, when data pooled from all seven trials were analyzed, total mortality in the treatment groups was 11% lower, and this reduction was statistically significant.

Intervention reduced the incidence of stroke deaths in the six of the seven studies for which an odds ratio could be estimated (Figure 2). This reduction was statistically significant in both the VA and HDFP studies. The same was true for the incidence of nonfatal stroke.

Treatment reduced the incidence of coronary heart disease mortality in four of the seven studies with untreated controls and in the HDFP (Figure 3). This reduction was statistically significant only in the European Working Party on Hypertension in the Elderly trial. In this trial, nominal significance was achieved for "cardiac deaths," a category including deaths from congestive heart failure as well as ischemic heart disease. The figures for nonfatal myocardial infarction were not reported separately. Pooled data analysis showed that treatment lowered coronary heart disease mortality by 8%, which was not statistically significant.

Results of these nine long-term randomized, controlled studies offer convincing evidence for benefits of therapy in terms of total mortality and stroke incidence, but benefits were, for the most part, attributable to an impressive reduction in stroke mortality. On the other hand, the evidence that

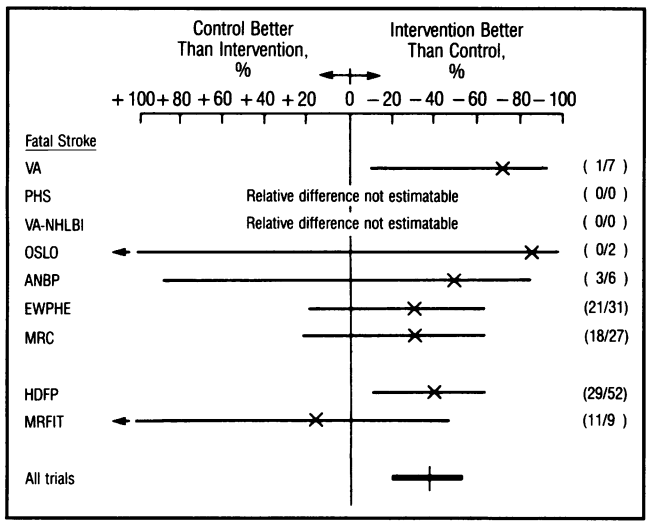

Figure 2.—Estimates, with approximate 95% confidence intervals, are shown for the relative difference in fatal stroke between intervention and control groups. The number of events (intervention/control) is given in parentheses (from MacMahon et al[65]). ANBP = Australian National Blood Pressure Study, EWPHE = European Working Party on High Blood Pressure in the Elderly, HDFP = Hypertension Detection and Follow-up Program, MRC = Medical Research Council Working Party, MRFIT = Multiple Risk Factor Intervention Trial, OSLO = Oslo Trial in Mild Hypertension, PHS = US Public Health Service Hospitals Cooperative Study Group, VA = Veterans Administration, VA-NHLBI = Veterans Administration–National Heart, Lung, and Blood Institute

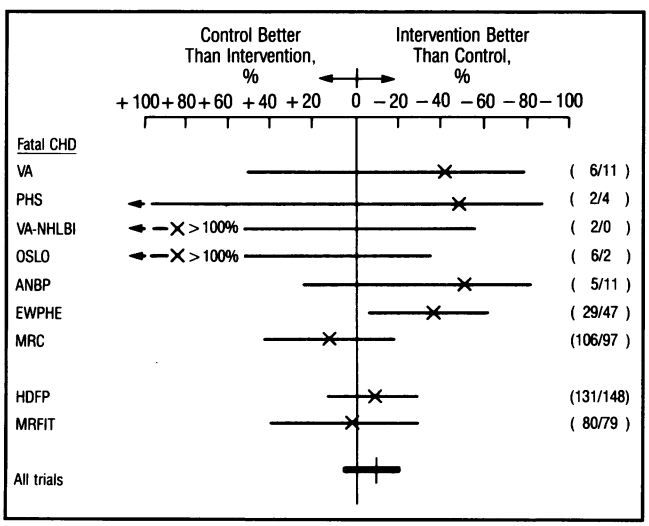

Figure 3.—Estimates, with approximate 95% confidence intervals, are shown for the relative difference in total coronary heart disease (CHD) mortality between intervention and control groups. The number of events (intervention/control) is given in parentheses. Data in the European Working Party on High Blood Pressure in the Elderly (EWPHE) were reported only as total cardiac mortality (from MacMahon et al[65]). ANBP = Australian National Blood Pressure Study, HDFP = Hypertension Detection and Follow-up Program, MRC = Medical Research Council Working Party, MRFIT = Multiple Risk Factor Intervention Trial, OSLO = Oslo Trial in Mild Hypertension, PHS = US Public Health Service Hospitals Cooperative Study Group, VA = Veterans Administration, VA-NHLBI = Veterans Administration–National Heart, Lung, and Blood Institute

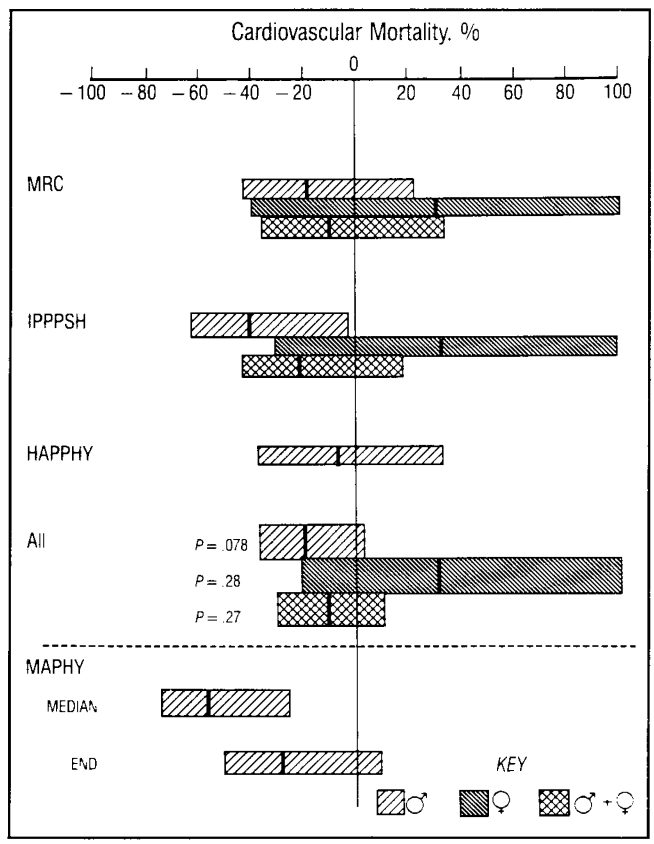

Figure 4.—Estimates, with approximate 95% confidence intervals, are shown for the relative difference in cardiovascular mortality among intervention and control groups by sex and by total study population in the Medical Research Council Working Party (MRC), International Prospective Primary Prevention Study in Hypertension (IPPPSH), and Heart Attack Primary Prevention in Hypertensives (HAPPHY) studies. Meta-analysis was used to determine pooled results of all three studies (All) by sex and by total study populations. The lower panel shows results for men in the Metaprolol Atherosclerosis Prevention in Hypertension (MAPHY) study (from MacMahon et al[65]).

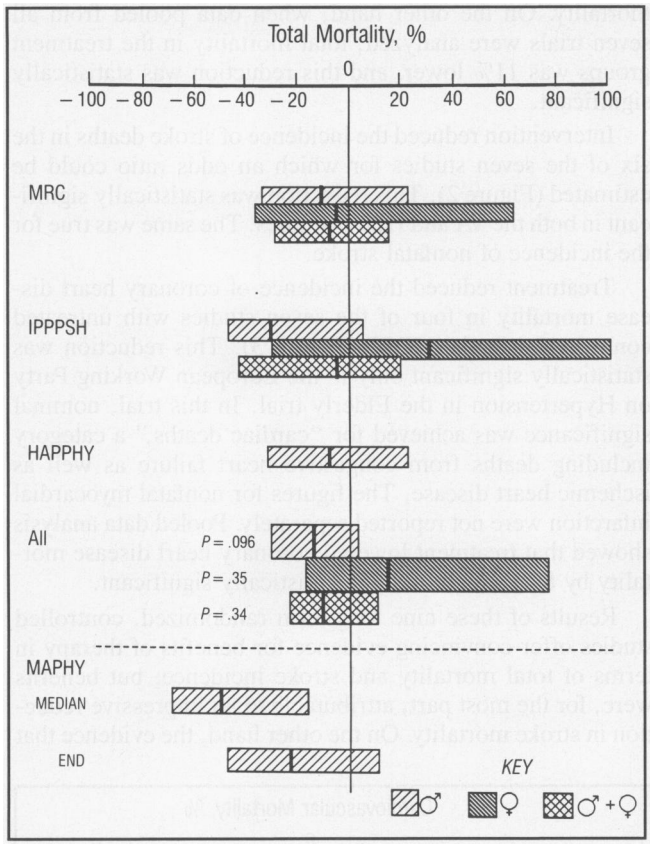

Figure 5.—Estimates, with approximate 95% confidence intervals, are shown for the relative difference in total mortality among intervention and control groups by sex and by total study population in the Medical Research Council Working Party (MRC), International Prospective Primary Prevention Study in Hypertension (IPPPSH), and Heart Attack Primary Prevention in Hypertensives (HAPPHY) studies. Meta-analysis was used to determine pooled results of all three studies (All) by sex and by total study populations. The lower panel shows results for men in the Metaprolol Atherosclerosis Prevention in Hypertension (MAPHY) study (from MacMahon et al[65]).

treatment prevents morbidity and mortality from coronary heart disease is unconvincing. A later report analyzed all available data from 13 unconfounded randomized trials of antihypertensive agents involving nearly 37,000 persons.[76] This report included eight of the nine trials in the MacMahon analysis (MRFIT was excluded because of a concomitant intervention on other risk factors) plus five others. The 13-trial analysis suggested a significant reduction ($P < .01$) in coronary heart disease events.

Three subsequent long-term clinical trials also evaluated the efficacy of blood pressure treatment to prevent complications of hypertension, bringing the total to 12 trials in the past decade. Despite the significant lowering of blood pressure reported in two of the three, the International Prospective Primary Prevention Study in Hypertension (IPPPSH)[77] and the Heart Attack Primary Prevention in Hypertensives (HAPPHY),[78] results failed to show any difference between diuretics and β-blockers in reducing total and cardiovascular mortality. Figures 4 and 5 compare cardiovascular and total mortality in the IPPPSH,[77] HAPPHY,[78] and Medical Research Council[68] trials with that in the controversial Metaprolol Atherosclerosis Prevention in Hypertension (MAPHY) study.[79] In all 12 recent trials, diuretics, β-blockers, or both were used to lower blood pressure. Moreover, the three latest studies (IPPPSH, HAPPHY, and MAPHY) compared the use of diuretics with that of β-blockers and did not include a placebo control group. Of these, only the MAPHY study showed a bottom-line difference between diuretics and β-blockers. In the Medical Research Council study, however, both diuretics and β-blockers produced better outcomes than placebo.

This review raises important questions: Why did individual studies fail to show benefits of blood-pressure lowering for coronary heart disease and total mortality? And why, even with meta-analysis, was minimal benefit shown for coronary heart disease? Some of the reasons may be as follows:

- The trials were too small. Even with pooling of data, clinically important effects on coronary heart disease (for example, a decrease of 15%) were not detected.
- The trials may have been too short; 5.6 years may not be long enough for blood pressure reduction to affect the incidence of atherosclerosis.
- The metabolic side effects of the drugs may have offset the benefits of blood pressure reduction. β-Blockers are known to reduce high-density–lipoprotein cholesterol levels and to increase low-density–lipoprotein cholesterol and triglyceride levels. Diuretics are known to increase total cholesterol and to decrease serum potassium and body magnesium levels.
- The widespread use of antihypertensive agents among control patients from these studies, particularly those using community control groups, may have reduced the estimates of true benefit.
- It has been proposed that differences in autoregulatory reserve and blood-oxygen extraction potential between the coronary and cerebral circulation may explain why antihypertensive treatment protects against stroke but not myocardial infarction.[80] This explanation is consistent with the report of a J-curve relation between death from myocardial infarction and treated diastolic blood pressure in hypertensive patients with concomitant coronary arteriosclerosis.[81]

Angiotensin-converting Enzyme

Is there any basis for thinking that ACE inhibitors might differ from diuretics and β-blockers? Is this question regulatory or only scientific? Worldwide, no regulatory agency requires that antihypertensive agents be shown to reduce morbidity and mortality to be licensed to treat high blood pressure. On the other hand, it is unlikely that any regulatory agency would permit an advertising claim that a particular drug provides cardioprotection in the absence of convincing data from one or more controlled trials designed to evaluate morbidity and mortality. Thus, in addition to answering the scientific question, there may be commercial interest in establishing that ACE inhibition reduces cardiovascular risk in hypertensive patients.

Before looking at the potential of ACE inhibitors in this regard, we should consider what diuretics and β-blockers do in addition to lowering blood pressure. We know that diuretics are effective in preventing or managing early congestive heart failure. We also know that they increase the incidence of ectopia and reduce renal blood flow. Whether or not they reverse left ventricular hypertrophy remains uncertain. β-Blockers have known cardioprotective effects in survivors of at least one myocardial infarction. Indeed, this finding formed the basis for the primary prevention studies (MRC, IPPPSH, HAPPHY) comparing diuretics and β-blockers. β-Blockers are known to reduce ectopia and to reverse left

ventricular hypertrophy; they may also reduce infarct size. On the other hand, they also reduce myocardial contractility and cardiac output, reduce renal blood flow, and affect related renal functions.

How does the use of ACE inhibitors compare with that of diuretics and β-blockers? They are as effective as thiazide diuretics and β-blockers in reducing blood pressure and maintain this effect without producing tolerance. This clinical efficacy is attributable to their unique humoral and hemodynamic effects, namely vasodilation without reflex activation of the sympathetic nervous system and without sodium retention; the most obvious consequences are no increase in heart rate and no edema. Additional evidence suggests that by unloading the left ventricle, ACE inhibitors can prevent damage or failure of the heart as a pump, can cause regression of left ventricular hypertrophy,[82] and can be effective in treating heart failure.[34,50,76]

By inhibiting endogenous angiotensin II formation and action, ACE inhibitors increase renal blood flow and reduce glomerular hydrostatic pressure while preserving the glomerular filtration rate.[83] Furthermore, in hypertensive patients with only modest renal dysfunction, long-term therapy with ACE inhibitors increases the glomerular filtration rate and renal blood flow and decreases renal vascular resistance.[84] Angiotensin-converting enzyme inhibitors may therefore exert a favorable influence on renal hemodynamics in the presence or absence of renal insufficiency.

But what of the morbidity and mortality from ischemic heart disease that diuretics and β-blockers have failed to prevent? Could ACE inhibitors prevent coronary atherosclerosis, ventricular arrhythmia, or sudden death? How do they influence the coronary circulation, and what is their effect in the presence of coronary disease? They can certainly remove hypertension as an atherogenic factor. Because they are lipid neutral and may suppress platelet aggregation in patients with essential hypertension,[85] they may have the potential to prevent coronary atherosclerosis. They neither activate the sympathetic nervous system nor deplete potassium; as a result, they may also have negligible potential for inducing malignant arrhythmias.[86] Indeed, both enalapril and captopril reduce the frequency of ventricular arrhythmias in congestive heart failure. Finally, ACE inhibitors may reduce myocardial oxygen demand and increase oxygen supply,[87] increase collateral blood supply to ischemic zones and decrease infarct size in dogs,[88] and prolong survival after myocardial infarction in rats.[89]

Do these data give us good reason to think that ACE inhibitors are superior to diuretics and β-blockers in reducing the risk of cardiovascular complications in patients treated for hypertension? Taken together, they suggest that ACE inhibitors may offer primary cardioprotection and may exert beneficial therapeutic effects in hypertensive patients with coronary heart disease. Are these data suggestive enough to compel us to consider a definitive long-term clinical trial that would have to be very large and thus very expensive? My answer is an unequivocal yes, both in terms of scientific importance and practical value for patients, to say nothing of the commercial consequences for manufacturers of this class of agents.

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